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One-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles promoted by nano-$TiCl_4.SiO_2$

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KEYWORDS

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Benzil;
One-pot synthesis;
Solvent free condition;
Supported Lewis acid.

Abstract Nano-$TiCl_4.SiO_2$ is an efficient, readily available and reusable catalyst for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, aromatic aldehyde and an amine in the presence of ammonium acetate. The one-pot procedure is very simple with good to excellent yields.

1. Introduction

The imidazole core is present in many molecules with biological activity [1], such as anti-allergy [2], anti-inflammatory [3], analgesic, antifungal, antimycotic, antibiotic, antiulcerative, antibacterial and antitumor [4]. In addition, many of the substituted diaryl imidazoles are known as potential inhibitors of the p38 MAP kinase [5]. Appropriately, substituted imidazoles are extensively used as glucagon receptors [6] and CB1 cannabinoid receptor antagonists [7], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [8], antibacterial [9] and antitumor [10] agents.

Recently, the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles has been catalyzed by silica gel or Zeolite HY [11], silica gel/$NaHSO_4$ [12], I_2 [13], $K_5CoW_{12}O_{40}.3H_2O$ [14], heteropolyacids [15], $HClO_4$–SiO_2 [16], $InCl_3.3H_2O$ [17], $ZrCl_4$ [18], $BF_3.SiO_2$ [19], DABCO [20], PEG-400 [21] and silica-bonded propylpiperazine *N*-sulfamic acid (SBPPSA) [22].

$TiCl_4.SiO_2$, as a powerful Lewis acid, is a liquid which is highly volatile, corrosive and difficult to handle. It hydrolyses to produce HCl in the presence of moisture. Silica-supported $TiCl_4$ is a mild solid Lewis acid that promotes acidic catalyzed organic reactions. This catalyst does not need special precautions for preparation, handling or storage, and it can be stored at an ambient temperature for months without losing its catalytic activity. This catalyst was previously applied for the production of polymers [23].

In continuation of our investigation into the application of solid acids in organic synthesis [19,24–26], we have applied Nano-$TiCl_4.SiO_2$ as an efficient catalyst for synthesis of 1, 2, 4, 5-triphenylimidazoles via the reaction of benzil, aldehydes, amine and ammonium acetate.

2. Results and discussion

Nano silica supported titanium chloride (nano-$TiCl_4.SiO_2$), as an efficient acidic catalyst, was prepared via a reaction of nano SiO_2 with $TiCl_4$. The dimensions of nanoparticles were observed with SEM. The particle sizes of the commercial silica gel and synthesized nano-$TiCl_4.SiO_2$ were about 24 and 41 nm, respectively (Figure 1).

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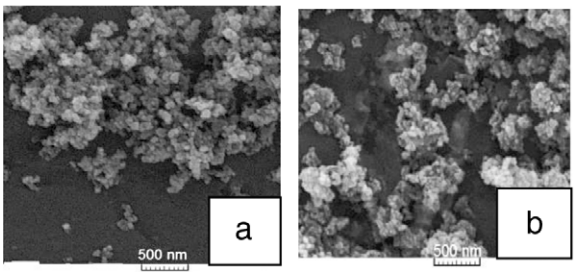

Figure 1: SEM photograph of (a) nano-SiO_2, and (b) nano-$TiCl_4.SiO_2$.

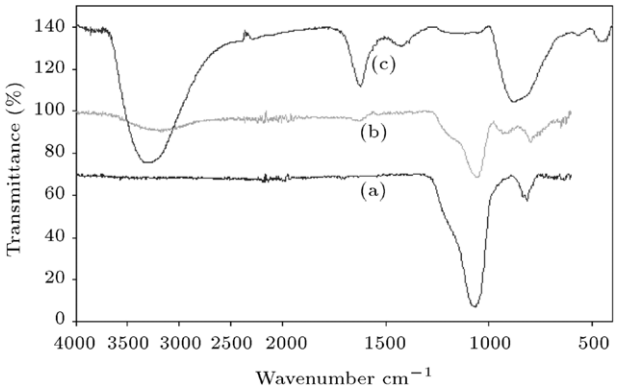

Figure 2: FT-IR spectrum of (a) nano-SiO_2, (b) nano-$TiCl_4.SiO_2$, and (c) $TiCl_4$.

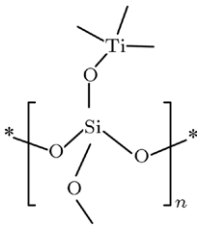

Figure 3: Suggested structure for nano-$TiCl_4.SiO_2$.

For identification of the structure of nano $TiCl_4.SiO_2$, we have studied the IR spectra of nano-SiO_2, nano $TiCl_4.SiO_2$ and $TiCl_4$ (Figure 2). In all of the spectra, very broad OH stretching bands are observed, with strong intermolecular hydrogen bonding. In FT-IR spectra of nano $TiCl_4.SiO_2$ and SiO_2, the absorption bands for Si–OH and Si–O–Si appear at $\sim$700 and $\sim$1100 cm^{-1}, respectively. The absorption band of Ti–Cl appears at 1600 cm^{-1} in the $TiCl_4$ spectrum. In the FT-IR spectrum of nano-$TiCl_4.SiO_2$, the O–Ti–Cl, Si–OH and Si–O–Si absorption bands are observed at 900, 700 and 1100 cm^{-1}, respectively [27,28]. We have suggested the following structure for nano-$TiCl_4.SiO_2$ (Figure 3).

Because the nano-$TiCl_4.SiO_2$ produces HCl in water, we have determined the concentration of the obtained acidic aqueous solution by titration. We have found that 0.1 g of catalyst produced a 0.0064 M acidic aqueous solution. For determination of the loading amount of Ti on 0.1 g of nano-$TiCl_4.SiO_2$, we have extracted Ti from the catalyst using an EDTA solution (0.004 M) at pH of 4. The standard solutions of titanium (IV) were prepared by dissolving a proper amount of $TiCl_4$ in acetone. Determination of the extracted Ti was carried out by an atomic absorption spectrometer with a hollow cathode lamp, at a wavelength of 346 nm, using C_2H_2/N_2O flame. The calibration equation for titanium was found as $A = 0.012C - 0.1895$ ($R^2 = 0.9998$). In this equation, A and C are the absorbance and concentration (mg L^{-1}) of titanium, respectively. The calculated loading amount of Ti in the catalyst is 7 mg g^{-1}.

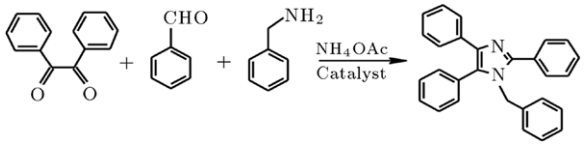

Figure 4: Synthesis of 1-benzyl-2, 4, 5-triphenyl-imidazole.

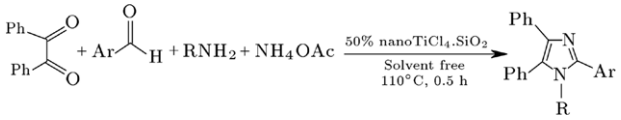

Figure 5: Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles in the presence of nano-$TiCl_4.SiO_2$ at 110 °C under solvent-free condition.

The reaction of benzaldehyde (2 mmol), benzyl amine (2 mmol), benzil (1 mmol) and ammonium acetate (2 mmol) was examined to optimize the reaction conditions (Figure 4). Reaction under different conditions in the presence of $TiCl_4.SiO_2$ revealed that the use of 0.3 g of 50% $TiCl_4.SiO_2$, solvent-free, at 110 °C was the best condition (entry 16, Table 1). We repeated the above mentioned reaction, using 50% nano-$TiCl_4.SiO_2$, and found that 0.1 g of 50% nano-$TiCl_4.SiO_2$ was necessary (entry 19, Table 1). To examine the reusability of nano-$TiCl_4.SiO_2$, in a solvent-free condition, after each run, the product was dissolved to $CHCl_3$ and filtered. The catalyst residue was washed with acetone and reused. Treatment with acetone removes the tar from the catalyst surface more efficiently (Table 1, entries 22 and 23). The catalyst was reusable, although a gradual decline was observed in its activity.

Next, benzil, various aldehydes and amines were used as substrates for the synthesis of 1, 2, 4, 5-tetra-substituted imidazoles (Figure 5 and Table 2). All products were known and characterized by FT-IR, ^{1}H-NMR, and the physical properties of those reported in the literature.

3. Conclusions

In conclusion, we have demonstrated a simple method for the synthesis of 1, 2, 4, 5-tetra-substituted imidazoles using 50% nano-$TiCl_4.SiO_2$ as a reusable, eco-friendly, inexpensive and efficient reagent. Short reaction times, high yield, scale-up, simplicity of operation and easy work-up are some advantages of this method.

4. Experimental section

The chemicals were used without any additional purification. The products were characterized by FT-IR, 1H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the ^{1}H NMR spectra. The absorption of titanium solutions was determined by an atomic absorption spectrometer; AVONA AA300. Also, the SEM of nano particles was determined with a VEGA/TESCAN scanning electron microscope.

4.1. *Preparation of nano-*$TiCl_4.SiO_2$ *and* $TiCl_4.SiO_2$

0.5 g (0.29 ml) of $TiCl_4$ was added drop wise to a mixture of 0.5 g of silica gel or nano-silica gel and 5 ml of chloroform.

Table 1: Acid catalyzed synthesis of 1-benzyl-2, 4, 5-triphenyl-imidazole.[a]

Entry	Catalyst (g)	Solvent	Condition	Time (h)	Yield[b] (%)	Reference
1	$TiCl_4.SiO_2$ (0.4)	Ethanol	r.t.	3	–	–
2	$TiCl_4.SiO_2$ (0.4)	*n*-Hexane	r.t.	3	–	–
3	$TiCl_4.SiO_2$ (0.4)	$CHCl_3$	r.t.	3	10	–
4	$TiCl_4.SiO_2$ (0.4)	CH_2Cl_2	r.t.	3	15	–
5	$TiCl_4.SiO_2$ (0.4)	$ClCH_2CH_2Cl$	r.t.	3	15	–
6	$TiCl_4.SiO_2$ (0.4)	Ethanol	Reflux	2.5	30	–
7	$TiCl_4.SiO_2$ (0.4)	*n*-Hexane	Reflux	2.5	30	–
8	$TiCl_4.SiO_2$ (0.4)	$CHCl_3$	Reflux	2.5	40	–
9	$TiCl_4.SiO_2$ (0.4)	CH_2Cl_2	Reflux	2.5	40	–
10	$TiCl_4.SiO_2$ (0.4)	$ClCH_2CH_2Cl$	Reflux	2.5	45	–
11	$TiCl_4.SiO_2$ (0.4)	Solvent-free	110 °C	2.5	75	–
12	30% $TiCl_4.SiO_2$ (0.4)	Solvent-free	110 °C	2	70	–
13	50% $TiCl_4.SiO_2$ (0.4)	Solvent-free	110 °C	1	85	–
14	60% $TiCl_4.SiO_2$ (0.4)	Solvent-free	110 °C	1	85	–
15	50% $TiCl_4.SiO_2$ (0.35)	Solvent-free	110 °C	1	84	–
16	50% $TiCl_4.SiO_2$ (0.3)	Solvent-free	110 °C	1	84	–
17	50% $TiCl_4.SiO_2$ (0.2)	Solvent-free	110 °C	1	75	–
18	50% Nano-$TiCl_4.SiO_2$ (0.2)	Solvent-free	110 °C	0.5	95	–
19	50% Nano-$TiCl_4.SiO_2$ (0.1)	Solvent-free	110 °C	0.5	94	–
20	50% Nano-$TiCl_4.SiO_2$ (0.1)	Solvent-free	90 °C	0.5	88	–
21	50% Nano-$TiCl_4.SiO_2$ (0.1)	Solvent-free	130 °C	0.5	95	–
22	50% Nano-$TiCl_4.SiO_2$ (0.1), 2nd run	Solvent-free	110 °C	1	70	–
23	50% Nano-$TiCl_4.SiO_2$ (0.1), 3rd run	Solvent-free	110 °C	1	58	–
24	I_2 (5 mol%)	Ethanol	75 °C	15 min	95	[13]
25	$K_5CoW_{12}O_{40}.3H_2O$ (0.1 mol%)	CH_2Cl_2	140 °C	2	95	[14]
26	PEG-400 (1.5 g)	Solvent-free	110 °C	6	86	[21]
27	DABCO (0.7 mol%),	*t*-BuOH	60–65 °C	12–15	92	[20]
28	$InCl_3.3H_2O$ (10 mol%)	Methanol	r.t.	8.3	82	[17]
29	37% BF_3/SiO_2 (21 mol%)	Solvent-free	140 °C	2	92	[19]
30	SBPPSA (0.25 g, 0.31 mmol of H^+)	Solvent-free	140 °C	1	95	[22]

[a] The used amount of benzaldehyde, benzyl amine, benzil and ammonium acetate is 2:2:1:2 mmol.
[b] Isolated yield.

The mixture was stirred for one hour at room temperature. The resulted suspension was filtered. The obtained solid was washed with chloroform and dried at room temperature.

4.2. General procedure for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles

Benzil (1 mmol), amine (2 mmol), aldehyde (2 mmol), ammonium acetate (2 mmol) and 50% nano-$TiCl_4.SiO_2$ (0.1 g) were placed in a round bottom flask. The obtained mixture was stirred at 110 °C for 30 min. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature, dissolved in ethanol and filtered to separation of the catalyst. By addition of water to the concentrated filtrate, the solid product appeared. The product was re-crystallized in hot ethanol. All products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

Table 2: Nano-$TiCl_4.SiO_2$ catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles.[a]

Entry	Ar	R	Yield (%)[b]	M.P. °C	Reference
1	C_6H_5	C_6H_5	82	217–218	[17]
2	C_6H_5	$C_6H_5CH_2$	84	162–165	[15]
3	C_6H_5	Cyclohexyl	64	168–169	[12]
4	C_6H_5	CH_3CH_2	70	115–116	[12]
5	4-ClC_6H_4	C_6H_5	81	148–151	[14]
6	4-ClC_6H_4	$C_6H_5CH_2$	79	162–163	[17]
7	2-ClC_6H_4	$C_6H_5CH_2$	83	141–142	[17]
8	4-OHC_6H_4	$C_6H_5CH_2$	68	134–136	[17]
9	4-$CH_3C_6H_4$	C_6H_5	73	185–188	[16]
10	4-$CH_3C_6H_4$	$C_6H_5CH_2$	91	165–168	[12]
11	4-$CH_3C_6H_4$	Cyclohexyl	75	163–164	[12]
12	3-$OMeC_6H_4$	$C_6H_5CH_2$	91	128–131	[17]
13	2-$NO_2C_6H_4$	$C_6H_5CH_2$	86	154–155	[17]
14	$(CH_3)_2CH$	$C_6H_5CH_2$	60	130–132	[17]

[a] The ratio of benzil (mmol): aldehydes (mmol): amine (mmol): ammonium acetate (mmol): nano-$TiCl_4.SiO_2$ (g) is 1:2:2.2:0.1.
[b] Isolated yield.

4.3. Selected spectroscopic data

1-Benzyl-2, 4, 5-triphenyl-imidazole: FT–IR(KBr) = 3020, 1598, 1490, 1435, 1382, 691, 754, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 5.13 (s, 2H), 6.82 (sbr, 2H), 7.2 (m, 4H), 7.35 (m, 4H), 7.4 (m, 4H), 7.6 (d, J = 8 Hz, 2H), 7.67 (m, 4H) ppm.

1-Cyclohexyl-2, 4, 5-triphenyl-imidazole: FT–IR(KBr) = 3053, 2929, 2852, 1599, 1498, 1440, 1381, 1335, 745, 691, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 0.8 (q br, J = 12 Hz, 1H), 1.1 (q br, J = 12 Hz, 2H), 1.6 (m, 6H), 1.9 (dbr, J = 12 Hz, 1H), 4 (t br, J = 12 Hz, 1H), 7.1 (m, 3H), 7.45 (m, 10H), 7.65 (m, 2H), ppm.

1-Benzyl-2-(4-chloro phenyl)-4, 5-diphenyl-imidazole: FT–IR (KBr) = 3100, 2900, 1601, 1497, 1448, 1028, 750, 696, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 5.1 (s, 2H), 6.8 (m, 2H), 7.25 (m, 7H), 7.4 (m, 6H), 7.6 (m, 4H), ppm.

2-(4-Chloro phenyl)-1, 4, 5-triphenyl-imidazole: FT–IR(KBr) = 3100, 2900, 1597, 1495, 1410, 1084, 836, 766, 696, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 6.85 (d br, J = 6 Hz, 2H), 6.95 (d br, J = 6 Hz, 2H), 7.05 (m, 11H), 7.2 (d, J = 6 Hz, 2H), 7.4 (d, J = 6 Hz, 2H), ppm.

1-Benzyl, 2-(3-Methoxy phenyl)-4, 5-diphenyl-imidazole: FT–IR (KBr) = 3027, 2900, 1601, 1577, 1481, 1217, 695, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 3.73 (s, 3H), 5.1 (s, 2H), 6.84 (m, 2H), 6.97 (m, 1H), 7.2 (m, 10H), 7.35 (m, 4H), 7.6 (d, J = 6 Hz, 2H), ppm.

1-Benzyl-2-(isopropyl)-4, 5-diphenyl-imidazole: FT–IR(KBr) = 3100, 2965, 1601, 1496, 1453, 1361, 1320, 750, 700, ^{1}HNMR (400 MHz, $CDCl_3$): δ: 1.2 (d, J = 6 Hz, 6H), 2.7 (m, 1H), 4.9 (s, 2H), 6.7 (d, J = 5.8 Hz, 2H), 7.1 (m, 11H), 7.3 (d, J = 5.8 Hz, 2H), ppm.

Acknowledgment

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